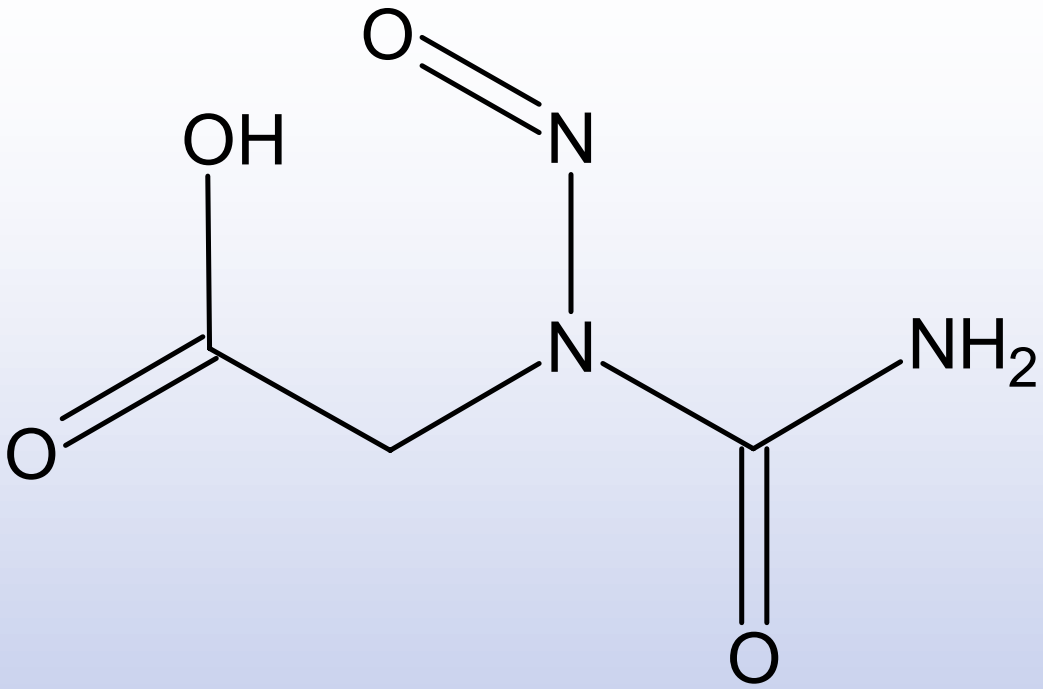
N-Carboxymethyl-N-Nitrosourea (CMNU)



Molecular Weight: 147.1 CAS Reg. No.: 60391-92-6

Occurrence of CMNU

- **CMNU is a naturally occurring compound with no known commercial uses.**
  - **CMNU is formed from reaction of glycocyamine and nitrite**
    - **Glycocyamine is the direct metabolic precursor of creatine, which is present in muscle (e.g., meat).**
    - **Nitrite is a compound produced endogenously, is added to cured meats as a preservative and color enhancer, and is a common drinking water contaminant.**
  - **CMNU may also form from reaction of nitrite and hydantoic acid, which is found in some plants.**
- **The typical daily dose of CMNU received by humans is unknown, but is expected to vary widely and depend primarily on nitrite and meat intake.**

Carcinogenicity of CMNU

- **Carcinogenicity in humans**
  - **No data**
- **Carcinogenicity in experimental animals**
  - **Two independent drinking water studies in rats**
    - **male rats (Buley *et al.*, 1979)**
    - **female rats (Maekawa *et al.*, 1983)**
  - **CMNU has not been tested in mice.**

Authoritative Body Activity

- NTP, US EPA, IARC, FDA, and NIOSH have not evaluated CMNU.

Tumors in male MRC Wistar rats receiving CMNU via drinking water, five days per week for 74 weeks (Buley *et al.*, 1979)

Tumor Site and Type		Treatment Group		
		untreated control	vehicle control	CMNU (260 ppm)
Gastrointestinal tract (GIT)	Squamous cell (SC) carcinoma of tongue	0/47	0/46	2/40
	SC papillomas of forestomach	2/47	2/46	3/40
	SC papillomas of the tongue or forestomach	2/47	2/46	5/40
	Adenocarcinoma of large and small intestines	0/47	0/46	4/40*
Skin	SC papillomas	Not reported	0/46	3/40
	SC carcinomas	Not reported	0/46	3/40
	SC papillomas or carcinomas	1/47	0/46	6/40*

* Significantly increased relative to vehicle controls (Fisher Exact Test, $p<0.05$)

Tumors and preneoplastic effects in female Donryu rats receiving CMNU via drinking water for 68 weeks (Maekawa *et al.*, 1983)

Tumor Site and Type		Dose, ppm				Trend[c]
		0	100	200	400	
Intestines (large and small)	Hyperplasia	0/36	4/40	12/38[b]	24/34[b]	p<0.0001
	Adenoma	0/36	4/40	15/38[b]	23/34[b]	p<0.0001
	Adenocarcinoma	0/36	1/40	9/38[a]	19/34[b]	p<0.0001
	Fibroma	0/36	0/40	1/38	0/34	p=0.42
	Fibro-or myosarcoma	0/36	0/40	0/38	3/34	p<0.05
Oral cavity	Squamous-cell papilloma or carcinoma	0/36	1/40	1/38	3/34	p=0.02

[a] p<0.01, Fisher Exact Test

[b] p<0.001, Fisher Exact Test

[c] Mantel-Haenszel trend test

Tumors and preneoplastic effects in female Donryu rats receiving CMNU via drinking water for 68 weeks (Maekawa *et al.*, 1983) -- Continued

Tumor Site and Type		Dose, ppm				Trend[c]
		0	100	200	400	
Mammary gland	Fibroma	0/36	1/40	2/38	0/34	p=0.52
	Fibroadenoma	9/36	27/40[b]	27/38[b]	10/34	p=0.65
	Adenoma	0/36	0/40	2/38	1/34	p=0.12
	Adenocarcinoma	0/36	1/40	0/38	0/34	p=0.69
	Total mammary tumors	9/36	28/40[b]	30/38[b]	11/34	p=0.54
	No. of mammary tumors per tumor-bearing rat	1.0	2.0	2.7	2.2	
Zymbal gland	Squamous-cell papilloma or carcinoma	0/36	0/40	1/38	3/34	p=0.006
Leukemia	Acute myelogenous	1/36	1/40	1/38	3/34	p=0.08

[b] $p<0.001$, Fisher Exact Test
[c] Mantel-Haenszel trend test

Summary of Animal Cancer Studies

Tumor site	Male rats (Buley *et al.*, 1979)	Female rats (Maekawa *et al.*, 1983)
Intestines	+	+
Skin*	+	
Zymbal's gland*		+ (trend only)
Oral cavity* or forestomach*	marginal	+ (trend only)
Mammary gland		unclear

* Squamous cell tumors

Genotoxicity of CMNU

CMNU is a direct acting mutagen and clastogen.

- **Bacterial assays**
  - **CMNU caused mutations in *S. typhimurium*, strains TA98, TA100, and TA1537, but not TA1535.**
  - **CMNU caused mutations in *E. coli*, strain H/r30R (wild type or repair deficient).**
- **Mammalian cells *in vitro***
  - **CMNU caused mutations, chromosomal aberrations in Chinese hamster lung fibroblast cells.**

Structure-Activity Comparisons

- **CMNU bears strong structural resemblance to other N-alkyl-N-nitrosourea compounds, such as N-ethyl-N-nitrosourea, which are carcinogenic in rodents, pigs and primates.**
- **CMNU, like methyl-, ethyl-, propyl-, butyl-, and isobutyl-N-nitrosourea, caused tumors of the intestines or oral cavity.**

Mechanism of carcinogenesis

- **Genotoxic mechanism likely**
- **CMNU is a carboxymethylating agent, which likely gives rise to carboxymethyl-DNA adducts (Harrison *et al.*, 1997).**
- **Other carboxymethylating agents are mutagenic and carcinogenic.**
  - Azaserine
  - N-Nitrosoglycocholic acid
  - N-Nitrosated peptides, such as N-(N'-acetyl-L-prolyl)-N-nitrosoglycine

CMNU: Summary

- **Animal evidence of carcinogenicity:**
  - **Intestinal tumors in two independent drinking water studies:**
    - **one in male Wistar rats**
    - **one in female Donryu rats**
  - **Squamous cell tumors of the skin in male rats**
  - **Squamous cell tumors of the oral cavity and Zymbal's gland in female rats (by trend test only)**
- **Other relevant evidence:**
  - **Mutagenic and clastogenic *in vitro***
  - **Structurally similar to well-recognized model carcinogens (e.g., ENU)**
  - **Other carboxymethylating agents cause cancer in rodents.**